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# Aberrant spontaneous brain activity in chronic tinnitus patients revealed by resting-state functional MRI

Yu-Chen Chen[a,1], Jian Zhang[a,1], Xiao-Wei Li[b], Wenqing Xia[c], Xu Feng[d], Bo Gao[e], Sheng-Hong Ju[a], Jian Wang[b,f], Richard Salvi[g], Gao-Jun Teng[a,*]

[a]Department of Radiology, Jiangsu Key Laboratory of Molecular and Functional Imaging, Zhongda Hospital, Medical School, Southeast University, Nanjing, China
[b]Department of Physiology, Southeast University, Nanjing, China
[c]Medical School, Southeast University, Nanjing, China
[d]Department of Otolaryngology, Zhongda Hospital, Medical School, Southeast University, Nanjing, China
[e]Department of Radiology, Yantai Yuhuangding Hospital, Yantai, Shandong, China
[f]School of Human Communication Disorders, Dalhousie University, Halifax, Nova Scotia, Canada
[g]Center for Hearing and Deafness, University at Buffalo, Buffalo, NY, USA

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ABSTRACT

*Objective:* The neural mechanisms that give rise to the phantom sound of tinnitus are poorly understood. This study aims to investigate whether aberrant spontaneous brain activity exists in chronic tinnitus patients using resting-state functional magnetic resonance imaging (fMRI) technique.
*Materials and methods:* A total of 31 patients with chronic tinnitus patients and 32 healthy age-, sex-, and education-matched healthy controls were prospectively examined. Both groups had normal hearing thresholds. We calculated the amplitude of low-frequency fluctuations (ALFFs) of fMRI signals to measure spontaneous neuronal activity and detect the relationship between fMRI information and clinical data of tinnitus.
*Results:* Compared with healthy controls, we observed significant increased ALFF within several selected regions including the right middle temporal gyrus (MTG), right superior frontal gyrus (SFG), and right angular gyrus; decreased ALFF was detected in the left cuneus, right middle occipital gyrus and bilateral thalamus. Moreover, tinnitus distress correlated positively with increased ALFF in right MTG and right SFG; tinnitus duration correlated positively with higher ALFF values in right SFG.
*Conclusions:* The present study confirms that chronic tinnitus patients have aberrant ALFF in many brain regions, which is associated with specific clinical tinnitus characteristics. ALFF disturbance in specific brain regions might be used to identify the neuro-pathophysiological mechanisms in chronic tinnitus patients.


## 1. Introduction

Subjective tinnitus refers to the phantom ringing, buzzing or hissing sensation that occurs in the absence of any corresponding external auditory source. Approximately 10%–30% of adults are influenced, while 5%–26% of adults rate their tinnitus as extremely annoying and 0.5% rate it as a severe and significant health care problem (Leske, 1981; Lockwood et al., 2002; Michikawa et al., 2010). Severe tinnitus can be extremely disruptive and debilitating leading many to seek medical treatment. By analogy with phantom limb pain, the phantom sound of tinnitus is often perceived as originating within the ear with hearing loss (Mühlnickel et al., 1998). The prevailing opinion, based on electrophysiological studies in animals and brain imaging studies (Kaltenbach et al., 2005; Lockwood et al., 1998), is that tinnitus is generated by aberrant firing patterns or high levels of spontaneous neural activity in the central auditory pathway and not the cochlea. Evidence in support of this view comes from clinical studies in which surgical section of the auditory nerve during acoustic neuroma surgery often fails to eliminate or reduce the severity of tinnitus in most patients (Baguley et al., 1992; Coad et al., 2001; Lockwood et al., 2001). Since tinnitus is often associated with cochlear hearing loss, it has been proposed that the loss of afferent input from the cochlea to the central auditory system can initiate tinnitus while central mechanisms are thought to play an important role in its maintenance (Kaltenbach et al., 2005). Previous animal studies have confirmed that the loss of afferent input could lead to an aberrant increase of spontaneous neural activity in auditory brain regions

* Corresponding author at: Department of Radiology, Zhongda Hospital, Southeast University, 87# Dingjiaqiao Road, Nanjing 210009, China.
*E-mail address:* gjteng@vip.sina.com (G.-J. Teng).
[1] Yu-Chen Chen and Jian Zhang contributed equally to this paper.

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(Kaltenbach et al., 2004; Norena and Eggermont, 2003). Hence, an abnormal increase of spontaneous activity in the cerebral neural system could potentially be perceived as tinnitus. However, the exact neuropathophysiological mechanism of tinnitus has not yet been fully elucidated.

Previous studies have investigated the auditory and non-auditory brain regions involved in the pathophysiological markers of tinnitus through magnetic resonance imaging (MRI) techniques using both structural and functional analytical strategies (Adjamian et al., 2009; Husain and Schmidt, 2014). Gray matter (GM) atrophy was detected in several brain regions of chronic tinnitus patients, such as the auditory cortex, inferior colliculus, anterior cingulate cortex and hippocampus using voxel-based morphometry (VBM) (Landgrebe et al., 2009; Leaver et al., 2011; Mühlau et al., 2006; Schecklmann et al., 2013b). Functional MRI (fMRI), especially the resting-state fMRI, has become a novel and widely used neuroimaging technique to explore the potential pathogenesis of various neuropsychiatric disorders. It is sensitive to low frequency (0.01–0.1 Hz) spontaneous fluctuations in the blood oxygenation level dependent (BOLD) signal with high spatial resolution and easy application (Biswal et al., 1995; Fox and Raichle, 2007; Ogawa et al., 1990). So far, several studies on tinnitus have demonstrated disrupted functional connectivity and networks changes between auditory and non-auditory brain areas prior to structural abnormalities using the resting-state fMRI (Husain and Schmidt, 2014). In a seed-based analysis, Burton et al. found the dissociation between activity in auditory cortex and visual, attention and control networks in bothersome tinnitus (Burton et al., 2012). Furthermore, tinnitus was observed to be associated with abnormal neuronal connectivity in multiple whole-brain networks involving auditory and non-auditory areas through independent component analysis or graph connectivity analysis (Maudoux et al., 2012; Schmidt et al., 2013). To date, previous fMRI studies on tinnitus have focused mainly on the aberrant functional connectivity networks among disparate brain areas.

As an alternative index to measure intrinsic brain responses at the baseline state, amplitude of low-frequency fluctuation (ALFF) reflects the intensity of regional neuronal activity (Biswal et al., 1995). This algorithm has been used as an effective method in assessing the altered neural activity of various neurological or psychiatric disorders, such as Alzheimer's disease, epilepsy, hepatic encephalopathy and schizophrenia (Chen et al., 2012; Hoptman et al., 2010; Wang et al., 2011; Zhang et al., 2010). Lv et al. found significant increased ALFF in bilateral precuneus and inferior frontal gyrus and decreased ALFF in multiple occipital areas of pulsatile tinnitus patients (Han et al., 2014). However, most tinnitus patients are non-pulsatile tinnitus with totally different mechanisms from the pulsatile tinnitus (Lockwood et al., 2002). Therefore, resting-state ALFF may be a useful index to reflect the abnormal neural activity in specific brain regions of chronic tinnitus patients.

Based on prior work and theoretical considerations, we hypothesized that tinnitus arises from aberrant spontaneous brain activity as reflected by alterations in ALFF within the central auditory system as well as non-auditory regions. Moreover, we speculated that aberrant ALFF activity would be correlated with specific tinnitus characteristics such as the tinnitus duration and tinnitus distress. The current study identified for the first time abnormal resting-state ALFFs that are linked to the perception of tinnitus, tinnitus duration and tinnitus distress.

**Table 1**
Characteristics of the participants.

| | Tinnitus patients ($n = 31$) | Healthy controls ($n = 32$) | $p$-Value |
|---|---|---|---|
| Age (year) | 41.9 ± 10.8 | 46.5 ± 12.6 | 0.120 |
| Gender (male:female) | 17:14 | 17:15 | 0.891 |
| Education levels (years) | 10.8 ± 2.2 | 11.2 ± 2.1 | 0.461 |
| Tinnitus duration (months) | 41.0 ± 36.2 | – | – |
| THQ score | 100.6 ± 73.4 | – | – |

THQ, tinnitus handicap questionnaire. Data are represented as mean ± SD.

## 2. Materials and methods

### 2.1. Subjects

We recruited 63 subjects (all right handed, with at least 8 years of education) made up of 31 chronic tinnitus patients and 32 healthy subjects through community health screening and newspaper advertisement from September 2011 to September 2013. The patients were group-matched in terms of age, sex and education. Thirteen patients reported a predominantly left-sided, 6 a predominantly right-sided tinnitus, and 12 patients described their tinnitus as bilateral or originating within the head. The severity of tinnitus and related distress was assessed by the Iowa version of the tinnitus handicap questionnaire (THQ) (Kuk et al., 1990). The patients were aged between 24 and 64 years (41.9 ± 10.8 years), with disease duration of 6–120 months (41.0 ± 36.2 months) and THQ overall scores of 17.41–278.15 (100.6 ± 73.4). The hearing threshold was determined by puretone audiometry (PTA) examination. All the participants had no hearing loss in any of 10 measured audiometric frequencies ranging from 250 Hz to 16 kHz (hearing thresholds < 25 dB). There were no statistically significant differences in auditory thresholds between both groups (see Supplementary Fig. 1 for average hearing thresholds). No included participants had accompanied symptoms such as depression and anxiety according to the Self-Rating Depression Scale (SDS) and Self-Rating Anxiety Scale (SAS) (overall scores < 50, respectively) (Zung, 1986; Zung, 1971). Patients with hyperacusis were excluded from the present study. Participants were also excluded if they suffer from Meniere's diseases or displaying hints of objective tinnitus, such as pulsatile tinnitus, or if they had a history of severe smoking, alcoholism, stroke, brain injury, Alzheimer's disease, Parkinson's disease, epilepsy, major depression or other neurological or psychiatric disorder/treatment, major medical illness (e.g., cancer, anemia, and thyroid dysfunction), MRI contraindications, and severe visual impairment. This study was approved by the Research Ethics Committee of the Affiliated Zhongda Hospital of Southeast University. All individuals provided written informed consent before their participation in the study protocol. Table 1 summarizes the characteristics of the chronic tinnitus patients and healthy controls.

### 2.2. MRI data acquisition

All imaging data were acquired using a 3.0 T MRI scanner (Siemens MAGENETOM Trio, Erlangen, Germany) with a standard head coil. Head motion and scanner noise were reduced using foam padding and earplugs. We used the earplugs (Hearos Ultimate Softness Series, USA) that could attenuate scanner noise by approximately 32 dB. Functional images were obtained axially using a gradient-echo planar sequence sensitive to BOLD contrast as follows: repetition time (TR) = 2000 ms; echo time (TE) = 25 ms; slices = 36; thickness = 4 mm; gap = 0 mm; field of view (FOV) = 240 × 240 mm; acquisition matrix = 64 × 64; and flip angle (FA) = 90°. Structural images were acquired with a T1-weighted 3D spoiled gradient-echo sequence as follows: TR = 1900 ms; TE = 2.48 ms; slices = 176; thickness = 1 mm; gap = 0 mm; FA = 90°; acquisition matrix = 256 × 256; FOV = 250 × 250 mm. During the scan, the subjects were asked to rest quietly with their eyes closed but to remain awake, and avoid thinking of anything particular.

### 1.3. MRI data analyses

Many studies have suggested that regional ALFF results could be influenced by brain volume (He et al., 2007; Oakes et al., 2007). Therefore, structural images were processed based on the VBM8 toolbox

(http://dbm.neuro.uni-jena.de/vbm). Briefly, cerebral tissues were segmented into GM, white matter (WM) and cerebrospinal fluid (CSF). Statistical parametric mapping was generated between tinnitus patients and healthy controls. Brain parenchyma volume was calculated as the sum of GM and WM volumes.

Data analyses were conducted using Data Processing Assistant for Resting-State fMRI programs (Chao-Gan and Yu-Feng, 2010), which is based on Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and resting-state fMRI data analysis toolkit (REST, http://www.restfmri.net). Slice-timing and realignment for head motion correction were performed. Any subjects with a head motion >2.0 mm translation or a 2.0° rotation in any direction were excluded. In this study, no subjects were excluded because of the exceeded head motion. After that, spatial normalization to the Montreal Neurological Institute template (resampling voxel size = $3 \times 3 \times 3$ mm$^3$) and smoothing with an isotropic Gaussian kernel (FWHM = 4 mm), detrending and filtering (0.01–0.08 Hz) were performed in order. ALFFs were finally calculated through the procedure described in previous studies (Zang et al., 2007). Briefly, time courses were first converted to the frequency domain using Fast Fourier Transform. The square root of the power spectrum was computed and then averaged squared across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF. For standardization purpose, the ALFF of each voxel was divided by the global mean ALFF value. The ALFF computations and further analyses were performed within a GM mask (Wang et al., 2011). Six head motion parameters and mean time series of global, WM and CSF signals were included in the regression analysis, to remove possible effects of such factors on the results.

### 2.4. Statistical analysis

#### 2.4.1. Clinical data analysis

Differences in clinical data between chronic tinnitus patients and healthy controls were analyzed using between-group *t*-test for means and $\chi^2$-test for proportions (statistical significance was set at $p < 0.05$).

#### 2.4.2. Within-group ALFF analysis

For within-group whole brain ALFF patterns, one-sample *t*-tests were performed on the individual ALFF maps in a voxel-wise way for patient group and healthy control group. Thresholds were set at a corrected $p < 0.05$, with multiple comparison correction using AlphaSim program (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf) determined by Monte Carlo simulation (Parameters were: single voxel *p* value = 0.05, a minimum cluster size of 85 mm$^3$, FWHM = 4 mm, within a GM mask corresponding to the AAL atlas (Forman et al., 1995)). The group-level ALFF maps were then visualized with the REST Slice Viewer in REST software.

#### 2.4.3. Between-groups ALFF analysis

For between-group analysis, a mask was created by combining the two ALFF maps of both groups, which were the result of one-sample *t*-tests. Two-sample *t*-tests were performed to calculate the ALFF difference between groups, with age, sex and head motion importing as covariates. The result was also determined by Monte Carlo simulation (Parameters were: single voxel *p* value = 0.05, a minimum cluster size of 85 mm$^3$, FWHM = 4 mm, within a GM mask corresponding to the AAL atlas), and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using statistical software (SPSS for Windows, version 17.0).

#### 2.4.4. Correlation analysis

To investigate the relationship between ALFF and clinical data of tinnitus patients, the mean ALFF values of the clusters with significantly alterations were extracted. Then the Pearson's correlation coefficients between ALFF and each clinical characteristic were analyzed by SPSS software, $p < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Structural data

Table 2 presents the comparisons of the brain volumes (GM volume, WM volume and brain parenchyma volume) between the chronic tinnitus patients and healthy controls. We did not find any significant changes in GM, WM or brain parenchyma volume in subjects with tinnitus compared to healthy controls.

### 3.2. ALFF data

The analyses of one-sample *t*-test revealed the ALFF maps in both tinnitus patients and healthy controls. Significant higher ALFF can be found in several brain regions, such as the bilateral cerebellum anterior/posterior lobe, thalamus, caudate nucleus, insular; and frontal, temporal, parietal, and occipital cortex (Fig. 1).

When using two-sample *t*-test analysis, chronic tinnitus patients had significantly increased ALFF values in the right middle temporal gyrus (MTG), right superior frontal gyrus (SFG) and right angular gyrus. In contrast, decreased ALFF values were observed in the left cuneus, right middle occipital gyrus and bilateral thalamus (Fig. 2 and Table 3).

### 3.3. Correlation analysis results

After one outlier for low ALFF value in right SFG was excluded, the ALFF value in right SFG was found to be positively correlated with the tinnitus duration and tinnitus handicap questionnaire (THQ) score, respectively ($r = 0.464$, $p = 0.010$; $r = 0.557$, $p = 0.007$). In addition, the ALFF value in right MTG was also positively associated with the THQ score ($r = 0.504$, $p = 0.004$) (Fig. 3). The correlations had been corrected for age and sex. The increased ALFF value in the right angular gyrus or decreased ALFF value in other specific regions was independent of tinnitus duration or THQ score. However, no significant correlations survived after Bonferroni correction.

## 4. Discussion

This present study was designed to identify the aberrant neural activity, as reflected by altered resting-state ALFF values, in subjects with tinnitus but without hearing loss. We identified abnormal ALFF changes within the central auditory pathway as well as non-auditory regions and found that these aberrant ALFF patterns were correlated with tinnitus characteristics such as the tinnitus duration and tinnitus distress.

Structural alterations could conceivably contribute to these functional abnormalities. The ALFF results could be influenced by whole brain or regional GM atrophy. However, we failed to detect any significant differences in whole brain volume between our tinnitus patients and healthy matched controls. Moreover, using a VBM region-of-interest (ROI) analysis (data not shown), we found no significant differences in regional GM volume in the specific brain regions with aberrant ALFF activity. Additionally, we performed ROI analyses in several brain

**Table 2**
Comparisons of the brain volumes between the tinnitus patients and healthy controls.

| | Tinnitus patients ($n = 31$) | Healthy controls ($n = 32$) | *p*-Value |
|---|---|---|---|
| Gray matter | 581.1 ± 25.5 | 575.0 ± 22.4 | 0.315 |
| White matter | 531.7 ± 24.7 | 527.8 ± 24.9 | 0.536 |
| Brain parenchyma | 1112.8 ± 32.5 | 1102.8 ± 37.7 | 0.264 |

Data are presented as mean ± SD.

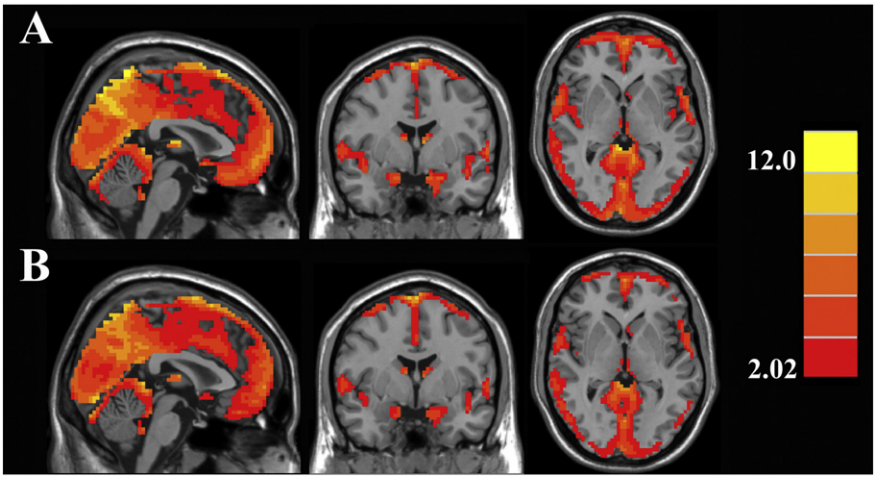


**Fig. 1.** Significant ALFF changes in whole brain using one-sample *t*-test in healthy controls (A) and tinnitus patients (B). Thresholds were set at a corrected $p < 0.05$, determined by Monte Carlo simulation. Note that the left side corresponds to the right hemisphere.

regions where others have found a decrease in GM volume (e.g., inferior colliculus, thalamus), but found no significant differences and therefore could not replicate these earlier findings of GM (Landgrebe et al., 2009; Mühlau et al., 2006) (data not shown). It is possible that the inherent heterogeneity of the tinnitus population may be one reason for the different results. Moreover, the MR technique and analytical method may also contribute to the differences. Thus, further explorations are still required to determine if GM alterations are uniquely due to tinnitus. Given the lack of change in GM volume, our results suggest that altered ALFF activity related to tinnitus can occur prior to any structural abnormalities. Remarkably, increased ALFF activity was found in the MTG (Brodmann's area 21) and angular gyrus (Brodmann's area 39) of tinnitus patients, brain areas linked to the auditory cortex. Using single photon emission computed tomography (SPECT), Farhadi et al. demonstrated that activity in associative auditory cortical areas, such as the MTG, was more closely correlated with the functional attributes of tinnitus than primary auditory cortex (Farhadi et al., 2010). Using Positron Emission Tomography (PET), Mirz et al. identified an increase of neuronal activity mainly in the right hemisphere with a focus on middle temporal regions (Mirz et al., 1999). In addition, higher tinnitus distress was correlated with enhanced ALFF values in the MTG, suggesting that ALFF changes probably reflect the impact of tinnitus perception. A correlation between higher brain metabolism in the MTG and tinnitus severity has already been documented in one PET study (Plewnia et al., 2007). Interestingly, the MTG and angular gyrus also belong to the default mode network (DMN). The DMN, consisting of nodes in the posterior cingulate/precuneus, bilateral MTG, angular gyrus and medial frontal gyrus, is most active at rest and shows reduced activity when a subject enters a task-based state involving attention or goal-directed behavior (Mantini et al., 2007; Raichle et al., 2001). Tinnitus as a condition involving the perception of a phantom auditory sensation, might lead to dysfunction of the DMN. Several functional connectivity studies using seed-based, ICA or graph theory analysis have found altered functional connectivity of the DMN related to the tinnitus distress compared with control groups (Burton et al., 2012; Maudoux et al., 2012; Schmidt et al., 2013). However, the source or type of

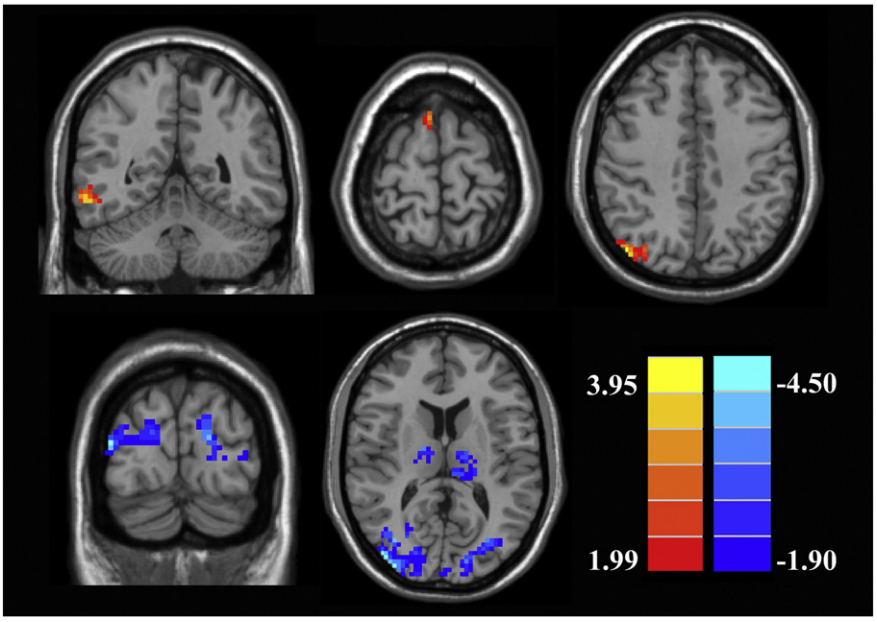


**Fig. 2.** Significant ALFF differences in tinnitus patients compared with healthy controls. Heat map (lower, right) shows areas of increased ALFF in top row (*t* values 1.99–3.95; red to yellow respectively) and decreased ALFF in bottom row (*t* values −1.90 to −4.50; dark blue to light blue respectively). Thresholds were set at a corrected $p < 0.05$, determined by Monte Carlo simulation. Note that the left side corresponds to the right hemisphere. Table 3 identified regions where significant increases and decreases occurred.

**Table 3**
Regions showing significant differences on ALFF of tinnitus patient group compared with healthy controls.

| Brain region | BA | Peak MNI coordinates x, y, z (mm) | Peak *t* score | Cluster size |
|---|---|---|---|---|
| (I) *Increased regions* | | | | |
| R middle temporal gyrus | 21 | 60, −51, −9 | 3.9250 | 87 |
| R superior frontal gyrus | 8 | 6, 15, 69 | 3.2846 | 86 |
| R angular gyrus | 39 | 45, −75, 42 | 4.3420 | 93 |
| (II) *Decreased regions* | | | | |
| L cuneus | 45 | −15, −87, 15 | −4.4015 | 262 |
| R middle occipital gyrus | 19 | 42, −87, 12 | −5.0516 | 292 |
| L thalamus | 77 | −15,−15,12 | −3.4703 | 153 |
| R thalamus | 78 | 15,−9,12 | −3.6783 | 95 |

A corrected threshold of $p < 0.05$ determined by Monte Carlo simulation was taken as meaning that there was a significant difference between groups. BA, Brodmann's area; MNI: Montreal Neurological Institute; L, left; R, right; cluster size is in $mm^3$.

aberrant neural activity within specific DMN regions due to tinnitus remains unclear. Our results indicate that increased ALFF activity in MTG and angular gyrus may be responsible for disrupting the DMN in tinnitus patients.

The vital role for the frontal cortex in subserving tinnitus mechanism has been postulated (Jastreboff, 1990) and previous neuroimaging studies have confirmed the involvement of frontal cortex for tinnitus (Lanting et al., 2009; Schecklmann et al., 2013a). Recently, Rauschecker et al. demonstrated structural and functional differences in ventromedial prefrontal cortex (vmPFC) between tinnitus patients and controls. Importantly, the observed BOLD response in vmPFC was correlated with tinnitus characteristics such as subjective loudness, indicating that frontal cortex may contribute to certain perceptual features of tinnitus (Leaver et al., 2011; Rauschecker et al., 2010; Seydell-Greenwald et al., 2012). In our resting-state fMRI study, increased ALFF activity in SFG was observed to be positively correlated with tinnitus duration and distress. In a task-fMRI study, Wunderlich et al. found the activation of the SFG due to acoustic stimulation in a pitch discrimination task, suggesting the perception of auditory inputs in a more emotional context in tinnitus (Wunderlich et al., 2010). Another research revealed that the left medial SFG was activated by laser stimulation of the tympanic membrane (Siedentopf et al., 2007). While it is difficult to establish conclusive interpretations of our results, we suggest that the SFG may be responsible for the integration of multi-sensory information, including the auditory sensation and pathophysiology of tinnitus perception. However, correlation analyses were not significant after the multiple comparison correction because of the stringent standard. Nevertheless, these results could provide some insights for future studies.

By contrast, several brain regions, including the visual areas and thalamus, showed reduced ALFF values, which was an unexpected finding. We speculate that the connections between auditory and visual regions make it possible to alter the brain activity in the visual areas (Cate et al., 2009; Kaltenbach et al., 2004). This is consistent with prior fMRI studies showing negative correlations of functional connectivity between auditory and visual resting-state networks in tinnitus patients (Burton et al., 2012; Maudoux et al., 2012). One possibility is that the phantom sounds might act to decrease spontaneous activity in visual areas because of the salience of the tinnitus perception. The thalamus is the main relay center between the cerebral cortex and various peripheral sensory systems. The primary auditory thalamic inputs to the auditory cortex originate in the medial geniculate body while other nuclei contribute to the auditory thalamocortical projection (Hackett, 2011). Tinnitus sufferers were found to have disrupted WM integrity in tracts involving connectivity of the thalamus (Aldhafeeri et al., 2012). Llinas and Steriade raised an influential thalamocortical dysrhythmia model, postulating that tinnitus is due to the disruption of coherent oscillatory activity between the thalamus and cortex. This model also appears to suggest that tinnitus without hearing loss may be associated with abnormal gamma activity, which has been supported by magnetoencephalography (MEG) studies (Llinás et al., 2005; Llinás et al., 1999; Steriade and Llinás, 1988). Nevertheless, the underlying mechanisms by which the tinnitus results in the aberrant connectivity between auditory and non-auditory systems still require further investigation.

Surprisingly, all the increased ALFF values were lateralized to the right hemisphere region in tinnitus patients. Asymmetry for the tinnitus patients has been reported both structurally and functionally (Geven et al., 2014; Landgrebe et al., 2009; Schecklmann et al., 2013a; Smits et al., 2007). Previous PET studies have revealed higher resting-state metabolic activity in right associative auditory brain areas (Geven et al., 2014). Other ROI analysis demonstrated an overactivation of the left Heschl's gyrus independent of tinnitus laterality and anatomical hemispheric differences (Schecklmann et al., 2013a). Other studies also confirmed the left-lateralization in tinnitus (Arnold et al., 1996; Geven et al., 2014; Langguth et al., 2006). The inconsistencies between studies might be due to the different neuroimaging methods used to investigate tinnitus or heterogeneity of the tinnitus patients. Therefore, further studies are needed to determine if the observed right-lateralization of ALFF is related specifically to tinnitus or some other factors.

Our study has several limitations. First, the study is cross-sectional with a relatively small sample size. Thus, it is difficult to make direct causal inferences regarding the relationships between the aberrant ALFF and tinnitus characteristics. Therefore, further longitudinal fMRI studies would be beneficial to establish the causal relationships. Second, partly due to a limited sample size, we did not make a subgroup comparison between the left-sided, right-sided and bilateral tinnitus. However, even tinnitus subgroups with similar clinical characteristics differ in their underlying pathophysiology mechanisms (Møller, 2007). Moreover, Lockwood et al. tested the patients who could modulate their tinnitus with oral facial maneuver and eye gaze (Lockwood et al., 2001;

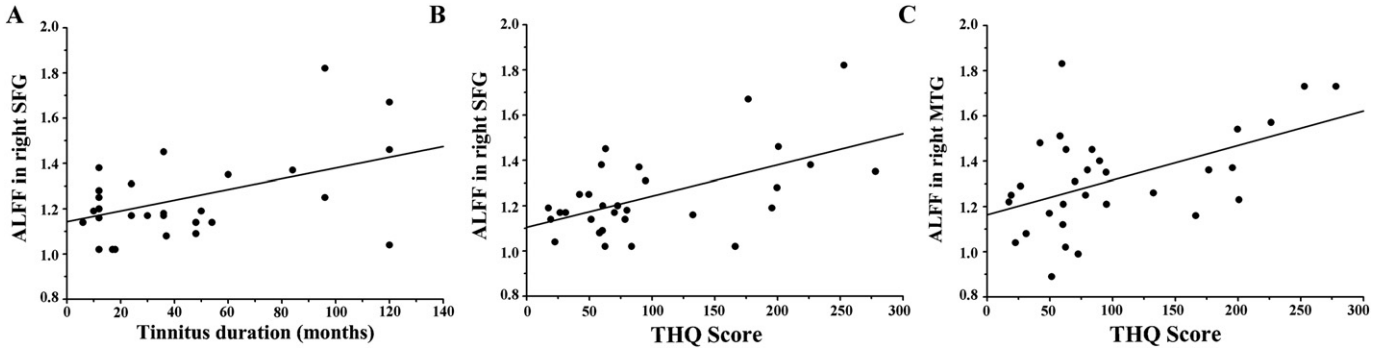


**Fig. 3.** Correlations between tinnitus duration, THQ score and ALFF values in right SFG and MTG. (A) Correlation between the tinnitus duration and ALFF value in right SFG ($r = 0.464$, $p = 0.010$). (B) Correlation between the THQ score and ALFF value in right SFG ($r = 0.557$, $p = 0.007$). (C) Correlation between the THQ score and ALFF value in right MTG ($r = 0.504$, $p = 0.004$).

Lockwood et al., 1998). For within-group analyses, ALFF differences could be observed in patients focusing on tinnitus in contrast to resting state. However, in this study, we did not ask the participants to focus on their tinnitus to avoid activating attention networks that could not be activated in control subjects. Future within subject studies of this nature might prove fruitful. Furthermore, tinnitus is often accompanied by hyperacusis with the reported prevalence ranging from 25% to 79%, probably due to various definitions and questionnaires for hyperacusis (Dauman and Bouscau-Faure, 2005; Meeus et al., 2010). Gu et al. demonstrated that subjects with hyperacusis showed elevated activation in the auditory midbrain, thalamus, and the primary auditory cortex compared with normal controls (Gu et al., 2010). Song et al. found hyperacusis-associated resting-state pathological brain oscillations in tinnitus patients using source-localized quantitative electroencephalography (qEEG) (Song et al., 2014). Thus, patients with hyperacusis were excluded from the current study. Future studies with patients having both tinnitus and hyperacusis might prove to be informative. Since the tinnitus subjects with normal hearing thresholds could not represent the majority of chronic tinnitus patients, the role of chronic tinnitus accompanying hearing loss should also be considered in future explorations. Finally, we acknowledge that the ALFF is unlikely to directly reflect the spontaneous neural activity that is typically understood, such as spontaneous firing of neurons or local field potential. Previous studies suggest that low-frequency BOLD signal may be linked to synchronized activity among groups of neurons or neural oscillators (Helps et al., 2008; Penttonen and Buzsáki, 2003; Penttonen et al., 1999). However, the putative link between resting-state fMRI signal and neural spiking or field potentials still remains uncertain. Moreover, the concept of resting state is somewhat problematic in our study because the auditory pathway is likely to be activated by scanner noise which is nearly impossible to completely eliminate even with ear plugs or active noise reduction (Logothetis et al., 2009). This limitation should be taken into account when interpreting the resting-state fMRI data in auditory system-related researches.

## 5. Conclusion

Our results reveal that chronic tinnitus patients with normal hearing show aberrant resting-state ALFF activity. The aberrant ALFF patterns occur within the central auditory as well as non-auditory regions and are linked to duration and severity of tinnitus. Thus, aberrant resting-state ALFF patterns in tinnitus-related networks may lead to a better understanding of the pathophysiology of chronic tinnitus.

Supplementary data related to this article can be found online at http://doi.dx.org/10.1016/j.nicl.2014.09.011.

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